CHAPTER 1

Introduction

1.1 General Introduction to Natural Drug

Plants play an important role in human wellbeing since the dawn of civilization. Plants are not only important sources of food, shelter and clothing but also of fine chemicals, which find their applications in pharmaceutical industries across the world. Nature is a rich storehouse of herbal remedies to cure different ailments. In recent years the interest and the usefulness of medicinal plants has revived. This is due to their high effectiveness and less known side effects. Today world population is approaching six billion and with this rate of growth it is possible to become 8.5 billion by the year 2020. Global estimates specify that over $\frac{3}{4}$ of the five billion world population cannot manage to pay for the products of the western pharmaceutical industry due to poverty and have to depend upon the use of traditional medicine which are mainly derived from plants. To meet the domestic demand as well as enhancing export of herbal drugs, India is thus, in a place to exploiting this natural source. In developed and developing countries medicinal and aromatic plants are important natural reserve materials for therapeutic agents.$^1$

Medicinal plants were available even before existence of human being on the earth.$^2$ So the history of drugs is older than mankind.$^3$ A medicinal plant is any plant which, contains substance that can be used for therapeutic principle or which is a precursor for synthesis of
useful drugs.\textsuperscript{4} Herbal remedies and substitute medicines are used all over the world. In the ancient times herbs are represented as original sources of most drugs.\textsuperscript{5-7} The vast variety available in the plant kingdom has provided an endless source of medicinal plants which were in the past used in their crude forms as herbal teas, syrups, infusions, ointments, liniments and powders. Historical background of use of herbal remedies is evident back from some 60,000 years to a burial site in a cave in northern Iraq, which was uncovered in 1960.\textsuperscript{8} An analysis of the soil around the human bones exposed surprising quantities of plant pollen of eight species. Out of these, seven are medicinal plants and still used all over the herbal world.\textsuperscript{9}

For addition of efficacy of herbal drugs, improvement of chemistry and western medicine become helpful. Active substances of many species have been isolated and in some cases duplicated in the form of synthetic drugs.\textsuperscript{10} However, the synthetic preparation of some drugs is either unidentified or economically unrealistic. For this reason, scientists continue to search for and test little-known plants and preserve those are therapeutically efficient and crucial in fighting diseases. Herbal-derived substances have formed a base of commercial medication and nowadays used for the management of heart disease, high blood pressure, pain, asthma and other illnesses. Today a vast number of modern drugs are still developed from natural sources and 25\% of all prescriptions contain one or more active ingredients derived from plants.
1.2 Herbal medicines

India has one of the richest plants medical backgrounds in the world. Medicinal plants play an important task in the improvement of potent therapeutic agents. In the USA drug market, during 1950-1970 around 100 plants based new drugs were introduced. Antipsychotics, antihypertensive drugs like deserpidine, reserpine, reseinnamine, vinblastine and vincristine which are derived from higher plants. From 1971 to 1990 new drugs such as ectoposide, guggulsterone, teniposide, nabilone, plaunotol, artemisinin and ginkgolides are used all over the world. 2% of drugs were developed from 1991 to 1995 for an example; paciltaxel, toptecan, gomishin, irinotecan etc.

Drugs that are based on plant origine provide wonderful input to modern therapeutics; for example: serpentine isolated from the root of Indian plant Rauwolfia serpentina in 1953, which is used in the management of hypertension and lowering of blood pressure. Vinblastine isolated from the Catharanthu roseus is used for the cure of Hodgkins, choriocarcinoma, non-hodgkins lymphomas, leukemia in children, testicular and neck cancer. Vincristine is suggested for acute lymphocytic leukemia in childhood complex stages of Hodgkins, lymphosarcoma, cervical and breast cancer. Podophyllotoxin is a constituent of Phodophyllum emodi presently used against testicular, small cell lung cancer and lymphomas. Herbal drugs are used to treat skin diseases, tuberculosis, diabetes, mental illness, jaundice, and cancer. In the development of potent drugs so as to achieve faster results, medicinal plants can play an important role. Thus plant
derived drugs are useful in modern medicine by using plant material as native treatment in traditional systems of medicine. More than 64 plants posses’ antibacterial properties and additional more than 24 plants posses’ antidiabetic properties. *Daboia russellii* and *Naja kaouthia* have antidote activity. Lupeol acetate neutralize venom which is isolated from the root extract of Indian sarsaparilla *Hemidesmus indicus*. An active compound from the *Strychnos nuxvomica* seed extract, inhibite viper venom induced lipid peroxidation in experimental animals. Thus plant derived micromolecules have exact mechanism of action for inducing venom neutralization and this thought needs further attention, for the expansion of plant-derived therapeutic opponent against snakebite.

1.3 Market significance of herbal medicines

Taking into consideration demand for herbal medicines, it is predictable that the market for ayurvedic medicines is increasing at 25% per annum. Sales of medicinal plants have developed by nearly 30% in India. In the years 1997-2006 sales of medicinal plants is recorded as the peak rate of growth in the world. China and India are the biggest users of medicinal plants. Traditional Chinese Medicine uses more than 5000 plant species; India uses nearly 9000. According to Export Import Bank, the global market for medicinal plant related to do business having an escalation rate of 7-15 % per annum. China’s contribution in world herbal market is US$ 100 billion while India’s contribution is only US$2 billion. All the most important herbal-based pharmaceutical companies are performing a constant
development of about 25%. The popularity of traditional medicine is because these medicines have served as a source of alternative medicine, new pharmaceuticals, and healthcare products. Medicinal plants are essential for pharmacological research and drug development. Plant constituents are used in a straight line as therapeutic agents, also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds.¹⁶

1.4 Future scenario of herbal medicine market

It is predicted that almost three fourths of the herbal drugs used internationally were discovered following leads from local medicine. According to World Health Organization (WHO) around 25% of recent medicines are developed from plants; first used traditionally. Various others are synthetic derivatives developed from prototype compounds isolated from plants. Approximately, 70% modern medicines in India are developed from natural products. The fundamental uses of plants in medicine will persist in the future, as a resource of therapeutic agents and as raw material foundation for the extraction of semi-synthetic chemical compounds such as cosmetics, perfumes and food industries. The secure uses of plant derived products in cosmetic industry have gained reputation and this has improved public costs in the day by day maintenance of personal health and welfare. In the twin task as a source of healthcare and income, medicinal plants make an important involvement in the superior development process. The effectiveness of herbal drugs requires development of quality awareness in respect of the evaluation
related evidences, yet supplying the demand for botanicals and herbals is a successful business. Clearly the claim for plant derived products has increased worldwide. The demand is expected to grow in the years to come compleated by the expansion of sales of herbal supplements and remedies. So it is clear that scientists and pharmaceutical companies will be attracted towards China, India, etc. for their necessities, because they have the the majority number of medicinal plant variety and are the top exporters of medicinal plants.\textsuperscript{17}

India is one of the world’s 12 most important biodiversity centers with the presence of 45,000 different plant species. Out of these about 15,000-20,000 plants have excellent medicinal value. On the other hand only about 7,000-7,500 are used for their medicinal values by traditional communities.\textsuperscript{18}

In 1966 WHO has given a complete definition for Drug - “Drug is any substance or product that is used or is planned to be used to modify or explore physiological states for the benefit of the recipient”. In French drug means, Drogue-a dry herb.\textsuperscript{19} WHO defines herbal medicine as finished, labelled medicinal products that contain as active ingredients, the aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant materials consist of juices, gums, fatty oils and any other substances of this nature. Herbal medicines may include excipients in addition to the active ingredients.\textsuperscript{20} WHO has defined certain terms to provide uniformity and international receipt
for the evaluation and research on herbal medicine. Herbs are defined as crude plant material such as leaves, fruits, seeds, stems, wood, barks, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.\textsuperscript{20}

Plant drugs are recognized to play a very important role in the management of liver disease. There are abundant plants and herbal formulations have hepatoprotective activity. Approximately 150 phytoconstituents from 101 plants have liver protecting activity. In India, more than 87 medicinal plants are used in various combinations for preparation of 33 patented herbal formulations.\textsuperscript{21-24}

The physiology of liver constitutes mostly in metabolism and excretion of different xenobiotics, environmental pollutants etc. But liver is bare to oxidative stress and free radicals. This results in the tissue necrosis and injury of this organ system. So numerous chances are been made to lookout liver from the free radical challenges. The free radicals are produced endogenously due to oxidative stress or the metabolism of different xenobiotics, pollutants etc. A diversity of species of free radicals is hydrogen peroxide anion, nitric oxide anion, superoxide anion, hydroxyl anion, etc. The undesirable effects of free radicals are seen as they interact with membrane of macro-molecules and denature them. In adding up, such covalent interaction may oxidize the lipids of the membrane. This lipid peroxidation initiates biochemical reactions leads to cellular necrosis. However, there are specific inherent antioxidant systems like superoxide desmustase, catalase etc. to destroy the free radicals and look after the organs. But
several times, the creations of free radicals are so high such that they may over command the inbuilt antioxidant systems and injure the cells.

The organ system like hepatic system is extremely sustible to attack by production of too much concentration of free radicals. Many drugs, chemicals, pollutants, may act as source of toxicity to this organ through mechanism mentioned above. Various antioxidants have been used to defend the organs from the free radical. The majority of antioxidants are of natural source. A various classes of phytococonstituents are well well-known to be antioxidant, example flavonoids, tannins, vitamin-E, vitamin-C etc. The especially important polyphenolic compound that are reported to have antioxidant and hepatic protective properties are quercetin, -tocopherol, -carotene, etc. Numerous researches are attempting to find out the option of using herbs having antioxidant principles as organ protective agents. In hunt of such agent, we had filed surveys and contact with native practitioners so as to recognize and evaluate the nearby available plants for their effectiveness as hepatoprotective agent.

Flavonoids are acknowledged to have anti-inflammatory, antioxidant, anti-allergic, hepatoprotective, antithrombotic, neuroprotective and anti-carcinogenic activities. Flavonoids are poly-phenolic compounds that are rich in fruits, vegetables, red wine, tea, and chocolate. They demonstrate a huge number of biological effects in-vitro and in-vivo after utilization of flavonoids containing
food. Epidemiologic studies show that increased utilization of flavonoids reduces the possibility of cardiovascular diseases and certain type of cancers.\textsuperscript{31}

Liver is the major and most complex internal organ in the body. It plays an important function in maintenance of internal environment as it shows variety in functions. It is concerned to the intermediary metabolism of proteins, fats and carbohydrates as well as in the synthesis of number of plasma proteins such as albumin, fibrinogen and in the production of various enzymes, formation and excretion of bile. It acts as storeroom depute for proteins, glycogen, various vitamins and metals. It also has a job in regulation of blood volume by transferring blood from portal to systemic circulation and its reticuloendothelial system mostly in immune mechanism. It plays vital role in detoxification and excretion of many endogenous and exogenous compounds. Hence any injury to liver or impairment of its function will have serious implication on the health of the person. Although viral infections are of main reason of hepatic injury. Xenobiotics, excessive drug therapy, environmental pollutants and chronic alcohol ingestion can also foundation of liver injury. Since it plays a fundamental role in processing, abolishing and disposition of foreign chemicals it is liable to their injurious effect.\textsuperscript{32}

Liver diseases are in the midst of the major diseases affecting mankind. In spite of the great advances made in allopathic medicine, no effective hepatoprotective medicine is available till date. Plant drugs are recognized to play a very important role in the managment
1.5 Need of the study

Nature has been a benefit to mankind; not only it nourishes us with food but also supply us medicinal plants that create valuable effect in treatment of various diseases. Traditionally, plants have been used to treat many ailments from tribe to tribe in different geographical locations.

The effectiveness of herbal drugs as well as its safety factor has made it to be extensively used by doctors nowadays. The modern medicine fails to effectively treat many malfunctions of liver or conditions like asthma, cardiovascular disorder etc. Antioxidants are well thought-out possible protective agents dropping oxidative damage to the human body. Therefore, there is an increasing attention in the substances exhibiting antioxidant properties that can be supplied to human and animal either in form of food or as specific pharmaceuticals. Considering the safety of synthetic antioxidants and effectiveness of natural antioxidants from edible materials, the expansion and use of more effectual antioxidants of natural origin is preferred.\textsuperscript{33} There are barely any confirmed remedies for the prevalent liver disorders among people. No drug has been developed in the modern system of medicine which may encourage the liver function, protect it from damage or help in the regeneration of hepatic cells. The only drugs, which are on hand for treatment of liver disorders, are corticosteroids and immuno-suppressive agents but their use is accompanied by serious side effects. There is a rising need for an
agent, which could defend the liver against damages.\textsuperscript{34}

Hence, in the present study, we were interested in carrying out a systemic phytochemical and biological evaluation of \textit{Leucas aspera} (Wild.) L. and \textit{Cassia tora} L. used traditionally for the treatment of liver disorders. The plant was evaluated for their hepatoprotective properties.

Phytochemical investigation will be a useful tool for the identification and authentication of the plant for additional research point of view. Antioxidants, which can scavenge free radicals, have a main role in biological systems. Antioxidants are emerging as prophylactic and therapeutic agents. Hence, the potent extract was also examined for antioxidant activity.

Therefore in the present study it is designed to assess the antioxidant and organ protective property of this plant. Hence taking into consideration it is thought that the present study is highly reasonable and more needful. Although several studies related to antimicrobial, anti-inflammatory and analgesic activities were carried out.

In view of the potential use of medicinal plants as a source of active constituents in eliciting novel drug molecules, the medicinal plants, \textit{Leucas aspera} and \textit{Cassia tora} are selected to study chemically and biologically.